IN THE CLAIMS:

Please add new claim 26 as shown in **Attachment C**.

REMARKS

By this Amendment, Applicants herein provide minor amendments to the specification and claims in order to make clear to the Examiner what the claimed invention is and in order to overcome minor problems with the reference to sequence ID numbers. Applicants amendments now overcome all outstanding rejections for the reasons as stated below.

As an initial matter, the specification was objected to on the basis that certain references to SEQ ID numbers were not included. Applicants' amendment now overcomes this objection in that the only sequences not having a sequence identifier were the primer sequences at page 20 and page 25 of the application, and these sequences have been deleted as unnecessary since the primers in the Examples are identified by their respective designations. All other sequences are properly referred to specification and are included in the sequence listing.

In the Official Action, the Examiner rejected Claims 3, 8 and 9 under 35 U.S.C. § 112 and 101. These rejections are respectfully traversed in that the Examiner appeared to be confused with regard to the coding sequence for the oligophrenin gene which has now been made clear in the amendments and amended sequence listing filed herewith. As set forth in the attached sequence listing, and as included in the original version of this listing (see the parent international application WO 99/31230), SEQ ID NO:26 contains a coding sequence from nucleotides 639 to 3047 which begins

with an ATG start codon and thus encodes the 802 amino acid sequence as shown in SEQ ID NO:27. Indeed, as reflected in Applicants' specification, SEQ ID NO:26 represents the cDNA fragment corresponding to the common open-reading frame (ORF) of the oligophrenin gene (see page 3, lines 4-5) that encodes the protein of 802 amino acids (see page 2, lines 15-16 of the published International application) as identified as SEQ ID NO:27. This coding region from SEQ ID NO:26 is now reflected in the new sequence listing attached hereto as well as in new claim 26.

Accordingly, the Examiners' objection under 35 U.S.C. §112 is respectfully traversed. Contrary to the Examiners' position that SEQ ID NO:26 is "but a fragment of an expressed sequence" and that the specification "does not teach what the nucleotide sequence encodes . . . or how this sequence could be used in a reproducible manner", the present application teaches that SEQ ID NO:26 represents the cDNA fragment corresponding to the common open-reading frame (ORF) of the oligophrenin gene and encodes the protein of 802 amino acids at the coding region at nucleotides 639 to 3047 of SEQ ID NO:26. The skilled artisan can thus readily use this information in a reproducible manner to obtain the claimed gene as well as to express the protein of SEQ ID NO:27 using the identified coding region in SEQ ID NO:26..

Moreover, as set forth in Applicants' specification, the present invention overcomes one of the major challenges for human genetics, namely to identify new causes of mental retardation, which, although present in about 3 % of individuals, have been unexplained in over half of all cases. In addition, X-linked mental retardation is acknowledged to be a major cause of severe learning difficulties, mostly in males. Despite recent advances in identifying genes, no gene prior to the present invention has been identified or cloned which was significantly involved in MRX, or non specific X-

linked mental retardation. By virtue of the present invention, the inventors have now identified and cloned the gene responsible for MRX, and this gene has been identified as the oligophrenin 1 gene which is the subject of the present claims. The nucleic acids of the invention are thus useful for the detection of an abnormality, such as a mutation, in the oligophrenin 1 gene, and such detection will be useful in permitting *in vitro* diagnosis and treatment of a neurological disorder associated with said abnormality.

Accordingly, the present claims are clearly proper under 35 U.S.C. §112, and clearly have utility under 35 U.S.C. § 101 for at least the reasons set forth above.

In light of the foregoing amendments and arguments, Applicants submit that the present application overcomes all prior objections, and is now in condition for immediate allowance. Such action is earnestly solicited.

Respectfully submitted,

February 20, 2003

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## ATTACHMENT A

Marked Up Replacement Paragraphs

At the following locations, a marked up copy of the replaced paragraph is provided.

**Page 21, line 14:**

YAC clones of the Xq12 locus were obtained from the UK HGMP Resource Centre. PAC clones were obtained from the German resource center (RZPD). Primer sequences corresponding to STSs are available in Genome Data Base. STSC16T3 is a 189 bp fragment amplified with the primers: C16T3F ~~(5' CACAGCAAGCAATAAGCACT 3')~~ and C16T3R ~~(5' TGTCTCCTGTGCTCTTTCCA 3')~~. Overlaps between clones and STS mapping were performed by a combination of STS/EST amplification and hybridization approaches.

**Page 25, line 16:**

The mutation to co-segregate with the mental retardation phenotype as shown on figure 4c was detected by denaturing gradient gel electrophoresis of PCR products corresponding to exon 19 of the oligophrenin 1 gene. Exon 19 was amplified by PCR with primers 19F ~~(5' GTT AAT CTT GCC CCT TTT CT 3')~~ and 19R ~~(5' Psoralen- TA GGA AGA CAG GTA GTG AGA AT)~~ yielding a 221 bp product. 10 µl of each amplified product was mixed with 10 µl of normal control PCR product. Heteroduplexes were generated by denaturing for 10 min, and subsequent reannealing for 45 min at 56°C. The samples were electrophoresed through a 25-65% denaturant 6% polyacrylamide gel for 7.5h at 60°C and 160V. The characteristic shifted profile displayed by the mutated allele allow an easy study of the familial segregation.

# ATTACHMENT B

Clean Replacement Paragraphs

At the following locations, replace the previously provided paragraph with the following clean paragraph(s).

**Page 21, line 14:**

YAC clones of the Xq12 locus were obtained from the UK HGMP Resource Centre. PAC clones were obtained from the German resource center (RZPD). Primer sequences corresponding to STSs are available in Genome Data Base. STSC16T3 is a 189 bp fragment amplified with the primers: C16T3F and C16T3R. Overlaps between clones and STS mapping were performed by a combination of STS/EST amplification and hybridization approaches.

**Page 25, line 16:**

The mutation to co-segregate with the mental retardation phenotype as shown on figure 4c was detected by denaturing gradient gel electrophoresis of PCR products corresponding to exon 19 of the oligophrenin 1 gene. Exon 19 was amplified by PCR with primers 19F and 19R yielding a 221 bp product. 10 µl of each amplified product was mixed with 10 µl of normal control PCR product. Heteroduplexes were generated by denaturing for 10 min, and subsequent reannealing for 45 min at 56°C. The samples were electrophoresed through a 25-65% denaturant 6% polyacrylamide gel for 7.5h at 60°C and 160V. The characteristic shifted profile displayed by the mutated allele allow an easy study of the familial segregation.

**ATTACHMENT C**

Clean New Claim

*Following herewith is a clean copy of the new claim.*

26. (New) Nucleic acid coding for the sequence of SEQ ID NO:27 comprising the sequence of from nucleotides 639 to 3047 of SEQ ID NO:26.